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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,268	MOEHLENBRUCK ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-102 and 125-128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-102 and 125-128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received July 15, 2008.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 1-81, 103-124 are canceled. Claims 82-102, 125-128 are pending and currently under examination.

Priority: The request for priority to US App. 09/545441, filed April 7, 2000, now US Patent 6,723,335, has been acknowledged.

Objections and Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 82-88, 91-102, 125-128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gan et al. (US 5964807; previously cited) in view of Mechanic (US 5854397; previously cited) as evidenced by Matsuzaki et al. (1996 Spine 21(2): 178-183; IDS 03/29/04).

Gan et al. disclose a method of manufacturing an implantable hybrid material comprising intervertebral disc cells and a biodegradable support substrate for placement into the intervertebral disc space (col. 5 lines 42-44). The intervertebral disc cells are nucleus pulposus cells extracted from the nucleus pulposus of lumbar discs, sacral discs, or cervical discs (col. 8

lines 1-7). Gan et al. further disclose the cells may be extracted from donor tissue (col. 8 lines 8-9) by surgical techniques (col. 8 lines 39-44). The extracted nucleus pulposus tissue can be treated with enzymes to disaggregate the cells (col. 8 lines 50-51). Further, the isolated intervertebral disc cells can be cultured alone or seeded onto a biodegradable substance and cultured together with the biodegradable substance for later implantation (col. 8 lines 58-61). To prepare the hybrid material, intervertebral disc cells are combined with biodegradable substrate materials, i.e. polymer foams (col. 7 lines 11-20, lines 65-66). Further, the hybrid material can also include factors to enhance cell growth, i.e. TGF-β, EGF (col. 8 lines 62-64). Gan et al. do not teach cross-linking.

Mechanic discloses a process for cross-linking a proteinaceous material, including collagen, collagen fibrils, and collagen matrices (col. 4 lines 15-16). According to Mechanic, the term proteinaceous material includes both proteins such as collagen and protein-containing materials such as tissue (col. 4 lines 19-20). Proteinaceous materials soaked in a first media solution and irradiated in a second are better cross-linked, show improved mechanical properties and decreased susceptibility to proteolytic degradation (col. 5 lines 1-4). Mechanic discloses solutions of high osmolality are generally used for the first media solution, i.e. sodium, chloride, potassium buffers, and Good's buffers, where in the osmolality have been increased by addition of a solute, such as sucrose (col. 5 line 10). In working examples 1-10, Mechanic discloses proteinaceous materials from different sources to be crosslinked, including pericardium tissue, collagen fibrils, and collagen (col. 8-13). In example 8, rat type I collagen was divided into six samples and each sample was placed in a dialysis bag with 300 mg NaCl (col. 12 line 35-37). Samples 5-6 were dialyzed into phosphate buffered saline pH 7.4 including 50% sucrose, and

0.2% methylene blue (col. 12, lines 40-41) and then exposed to a white floodflight while holding the temperature between 8° and 12°C (col. 12, lines 45-50).

It is known in the art that living, intact nucleus pulposus cells actively synthesize collagen and proteoglycan (p. 179) (Matsuzaki et al. 1996 Spine 21(2): 178-183; IDS 03/29/04).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Gan et al. by adding the cross-linking step of Mechanic et al. to the nucleus pulposus tissue culture of Gan et al. for a method of manufacturing an implantable material comprising nucleus pulposus tissue and a biodegradable support substrate for placement into the intervertebral disc space (claims 82-88, 91-100). The motivation to do so is given by Mechanic, which teaches cross-linking tissue and/or collagen results in a stable, bio-product that resists in vivo degradation and calcification when implanted; therefore, one of ordinary skill would expect to be successful in manufacturing a more structurally stable disc implant by cross-linking the nucleus pulposus cells of Gan et al. since it is known in the art that said cells synthesize collagen.

It would also have been obvious to one of ordinary skill in the art at the time the invention was made to add an additional therapeutic substance, i.e. TGF-β, to the disc implant manufactured by the method of Gan et al. in view of Mechanic (claims 101-102, 125). The motivation to do so is given by Gan et al., which teach that additional therapeutic substances can be added to the nucleus pulposus hybrid implant and may enhance growth of intervertebral disc cells in the recipient.

In their remarks, Applicants assert (1) Mechanic fails generally to teach a method of manufacturing an intervertebral disc implant and, as noted by the Examiner, specifically "does not teach nucleus pulposus tissue." (2) Gan teaches the use of donor nucleus pulposus *cells,* but not tissue comprising an extracellular matrix component harvested from the donor. Although Gan notes "tissue may be extracted from the nucleus pulposus of lumbar discs, sacral discs and cervical discs," that tissue, including extracellular matrix components thereof, subsequently is discarded to obtain isolated nucleus pulposus cells (col. 8, lines 50-61). These isolated cells are then combined with materials intended to substitute for the discarded nucleus pulposus tissue from which they were isolated and/or are cultured *(ibid.).* Thus, Gan teaches away from the use of "an extracellular matrix component harvested from the donor." (3) Matsuzaki does nothing to redirect the skilled artisan toward such a use, but simply confirms the prophetic disclosure of Gan regarding the ability of isolated nucleus pulposus cells to synthesize collagen (col. 11, lines 15-22). Moreover, any collagen synthesized by the isolated nucleus pulposus cells of Gan would *not* be an extracellular matrix component harvested from a donor. Applicant's arguments have been fully considered but they are not persuasive.

(1) The Mechanic reference is used to remedy the deficiency of Gan et al. (i.e., cross-linking collagen). In the Office action of May 30, 2008, it was noted that the rejection of the instant claims under 35 U.S.C. 103(a) has been amended from being unpatentable over Mechanic in view of Gan et al. to being unpatentable over Gan et al. in view of Mechanic.

(2) Applicants continue to assert that Gan et al. teach the use of donor nucleus pulposus cells, but not tissue comprising an extracellular matrix component harvested from the donor and

that these isolated cells are then combined with materials intended to substitute for the discarded nucleus pulposus tissue from which they were isolated and/or cultured.

Applicants are again referred to column 8 of Gan et al. Gan et al. disclose intervertebral disc cells are isolated from tissue extracted from the nucleus pulposus of lumbar discs, sacral discs and cervical discs. The isolated cells are primarily nucleus pulposus cells which may be combined with a biodegradable substrate and implanted into the evacuated nucleus pulposus (col. 8 lines 50-58). However, Gan et al. further disclose that alternatively, the isolated nucleus pulposus cells can be cultured alone or seeded onto a biodegradable substrate and cultured together with said substrate for implantation (col. 8 lines 58-61). Cells may also be incubated alone in a tissue culture medium (col. 8 lines 62-67). Since Gan et al. disclose that the donor nucleus pulposus cells can be cultured alone, which one of ordinary skill would recognize that when said cells are cultured alone, the isolated nucleus pulposus cells will grow and develop into nucleus pulposus tissue, which may or may not be used with a biodegradable substance for the manufacture of a disc implant. Therefore, even if tissue and extracellular matrix components are destroyed and/or discarded to isolate the donor nucleus pulposus cells, one of ordinary skill would recognize that cells cultured in tissue culture medium will grow to become tissue, including synthesizing any components that are necessary to develop into a tissue structure (i.e. extracellular matrix components). As previously noted, the term "tissue" as defined in the art, is an association of cells bound together by cell walls (plants) or extracellular matrix (animals) that performs a particular function. This is further evidenced by Matsuzaki et al. (1996 Spine 21(2): 178-183; IDS 03.29.04), which disclose that living nucleus pulposus cells actively synthesize proteoglycan and collagen (p. 179). Therefore, one of ordinary skill would recognize that if

cultured alone, the isolated nucleus pulposus cells of Gan et al. will expand into nucleus pulposus tissue, which can be used with a biodegradable substance for the manufacture of a disc implant. Further, as evidenced by Matsuzaki et al. (1996 Spine 21: 178-183; IDS 03/29/04), since it is known that living nucleus pulposus cells synthesize collagen, it would be reasonable for one of ordinary skill to contemplate cross-linking the nucleus pulposus cells, and not to cross-link the biodegradable substance (as suggested by Applicants in their remarks) since cross-linking is recognized in the art as a method of stabilizing a protein matrix and preserving its structure and integrity.

Therefore, Gan et al. do not teach away from the use of "an extracellular component harvested from the donor." The extracellular component would be naturally present as the donor nucleus pulposus cells grow and expand into tissue, and would be an "extracellular component from the donor."

(3) The collagen synthesized by the isolated nucleus pulposus cells of Gan et al. would be an extracellular matrix component harvested from a donor since said cells were harvested from a donor and said cells will naturally synthesize collagen and proteoglycan.

For these reasons, the claims remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gan et al. in view of Mechanic.

Claims 89-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gan et al. (US 5964807; previously cited) in view of Mechanic (US 5854397; previously cited) in view of Moore et al. (US 6350732; previously cited, IDS 11/03/06). The teachings of Gan et al. in view

of Mechanic are outlined above. Neither Gan et al. nor Mechanic teach extracting lipids from a collagenous tissue sample.

Moore et al. teach a method for extracting lipids from collagenous tissue samples for the purpose of storing and preserving the tissue sample and the product of that method (col. 1 lines 29-35).

It would have been obvious to one of ordinary skill in the art to extract lipids from the nucleus pulposus matrix manufactured by the method of Gan et al. in view of Mechanic (claims 89-90). The motivation to do so is given by Moore et al., which teach that extracting lipids from collagenous tissue samples will allow the product to be better preserved and stored for longer periods of time. One of ordinary skill would recognize that nucleus pulposus cells and/or tissue that are better preserved would cause less complications when implanted in the body.

The reasons for maintaining the Gan et al. and Mechanic references are the same as noted above.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/

Primary Examiner, Art Unit 1656

September 19, 2008